Revised Cumulative Risk Assessment: Organophosphorous Pesticides

Anna Lowit, Ph.D.
Toxicologist
Health Effects Division
Office of Pesticide Programs

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OP CRA Science Team

- Vicki Dellarco
- Elizabeth Doyle
- Jeff Evans
- David Hrdy
- David Miller
- Kathy Monk
- Steve Nako
- Stephanie Padilla
- Randolph Perfetti
- William O. Smith
- Woodrow R. Setzer
- Nelson Thurman
- William Wooge
- Plus Many, Many Others

Overview of Presentation

- History of OP CRA
- Hazard & Dose-Response
- Food, Drinking Water, Residential Exposure
- Cumulative Risk Results
- What's Next?

Brief History of Cumulative Assessment in OPP

- Food Quality Protection Act, 1996

  Requires EPA to take into account when setting pesticide tolerances

  "*available evidence concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity.*"

Public Participation Process

- 6 Public Technical Briefings
- Tolerance Reassessment Advisory Committee (TRAC)
- Committee to Advise Reassessment and Transition (CARAT)
- Numerous Science Advisory Panel meetings
- Preliminary assessment – public comment
- Revised assessment –public comment

How We Got There: SAP Advice Dose-Response and Hazard

- **March 1997.** Common Mechanism Guidance
- **March 1998.** OP Common Mechanism of Toxicity
- **September 2000.** Endpoints and RPF's: A Pilot Study
- **September 2001.** Preliminary Hazard and Dose-Response

How We Got There: SAP Advice Exposure Assessment

- **September 1997.** Residential Scenarios
- **December 1997.** Drinking Water
- **March 1998.** Probabilistic for Dietary, Residential, and Common Mechanism
- **July 1998.** Estimating Pesticide Concentrations in Drinking Water
- **May 1999.** Statistical Methods for Acute Dietary and Drinking Water
- **September 1999.** Residential
- **March 2000.** Models for Dietary and Drinking Water
- **June 2000.** Drinking Water Survey
- **September 2000.** Residential and Dietary Models and Drinking Water
- **March 2001.** Dietary Model

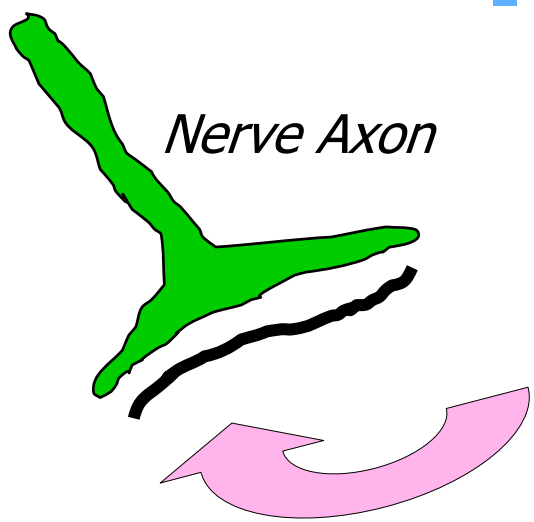
How We Got There: SAP Advice Assessment Methodology and Other

- **March 1997.** Aggregate Methodology
- **March 1998.** Probabilistic Risk Assessment Methodology
- **February 1999.** Aggregate Guidance
- **September 1999.** Cumulative and Aggregate Methodology
- **December 1999.** Cumulative Methodology
- **September 2000.** Risk Assessment Models
- **December 2000.** Case Study of 24 OP's and Cumulative Assessment Methodology
- **February 2002.** Preliminary OP Cumulative Risk Assessment
- **June 2002.** Sensitivity to Infants and Children

Hazard and Dose-Response Assessment

Identifying Common Mechanism Group: Organophosphorous Pesticides

- U.S. EPA 1999 Policy Paper



  - Inhibition of cholinesterase
    - Brain
    - Peripheral nervous system (e.g., nerves in diaphragm, muscles)
    - Surrogate/Indicator (RBC, Plasma)

Relative Potency Factor Method

- Relative toxic potency of each chemical is calculated in comparison to "index chemical"
- Exposure equivalents of index chemical are combined in the cumulative risk assessment

Index Chemical (Methamidophos)

- Criteria for selection of index chemical
  - Hazard considerations
    - Well-defined for common mechanism of toxicity
    - Toxicological profile for common effect consistent with chemical group across species/sexes/tissues
  - Dose-response considerations
    - Well characterized with no big gap between the NOAEL and the LOAEL
    - Strong database for all routes & durations of interest

Relative Potency Factor Method

- Calculate an Relative Potency Factor (RPF) for each chemical:

$$RPF = \frac{\text{Index Chemical}_{Potency}}{\text{Chemical n}_{Potency}}$$

Potency is portrayed as exposure equivalents to the index chemical

Relative Potency Factor Method

Chemical	RPF	Exposure (ppm)	Exposure Equivalents of Index (ppm)
A (index)	1	10	10
B	0.5	100	50
C	5	20	100
Total Exposure Equivalents of Index Chemical =			160 ppm

Hazard Endpoint in the Assessment

- Brain Cholinesterase Inhibition
  - Target tissue
  - Tighter confidence limits on potency estimates than for RBC and plasma
- Steady State Inhibition
  - Reflects actual human exposure
- Female rats
  - More sensitive for 5 OP pesticides

Data Collection

- Only ChE measurements from 21 days or greater were collected
- Oral Route:
  - Subchronic rat oral toxicity studies
  - Subchronic rat neurotoxicity studies
  - Chronic rat oral toxicity studies
  - Other nonguideline studies in rat
    - Range finding and Special studies

Data Collection

- Dermal Route:
  - 21/28 day dermal toxicity in rat or rabbits
  - 90-day dermal toxicity in rat
  - No dermal study was available for DDVP
- Inhalation Route:
  - 21/28 day inhalation toxicity in rat
  - 90-day inhalation toxicity in rat
  - Carcinogenicity in rat
  - No inhalation studies were available for bensulide and tetrachlorvinphos

Measure of Relative Potency

- Oral Route - BMD_{10}
  - The dose at which cholinesterase activity is reduced by 10% compared to the background level of cholinesterase activity
- Dermal and Inhalation Routes: CELs
  - Not modeled - Limited availability of studies
  - Comparative Effect Levels (CELs) were used
    - Comparative effect levels defined as treatment dose ≤ 15% ChEI, generally NOAELs for female brain ChEI

Point of Departure (PoD)

- **PoD**
  - Point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical

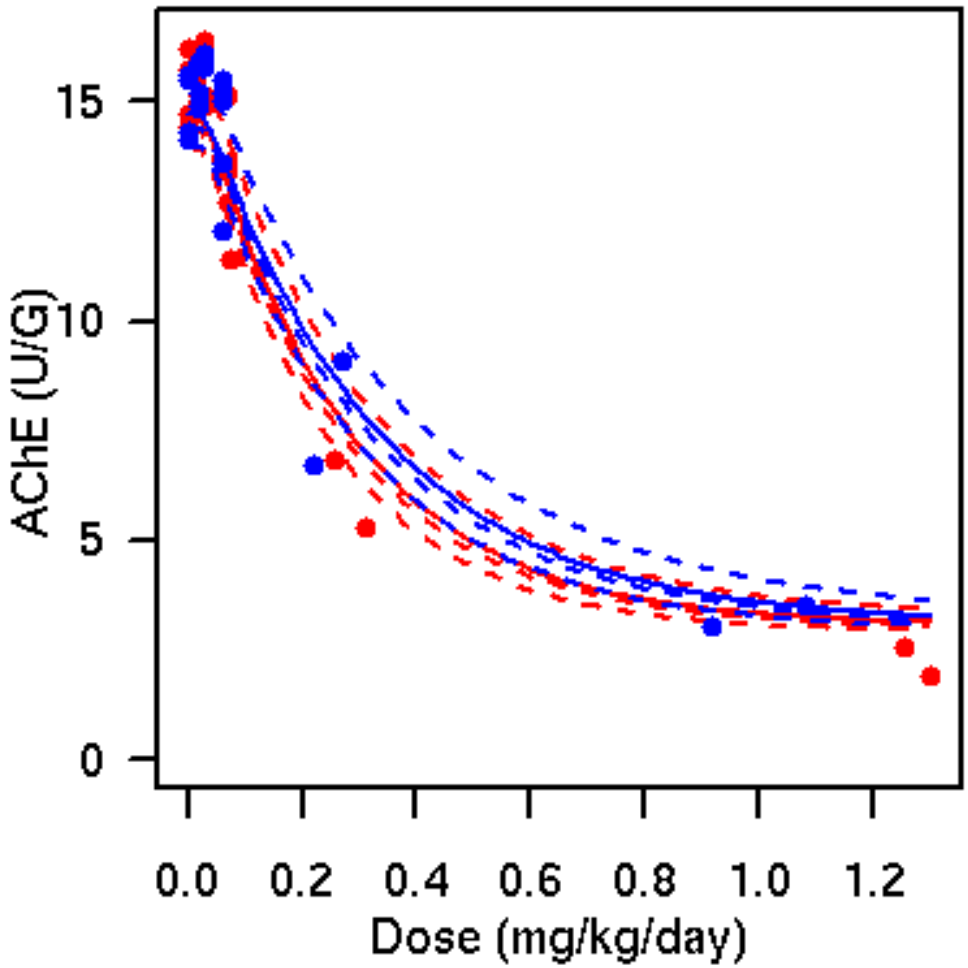
- **HAZARD X EXPOSURE = RISK**
  - Value used with exposure information to determine risk associated with environmentally relevant human exposures

- **BMD_{10}**
  - This is the point at which cholinesterase inhibition can be reliably said to have changed by 10% due to dosing

Method for Modeling ChE Data

$$y = A[P_B + (1-P_B)e^{-m \times Dose}]$$

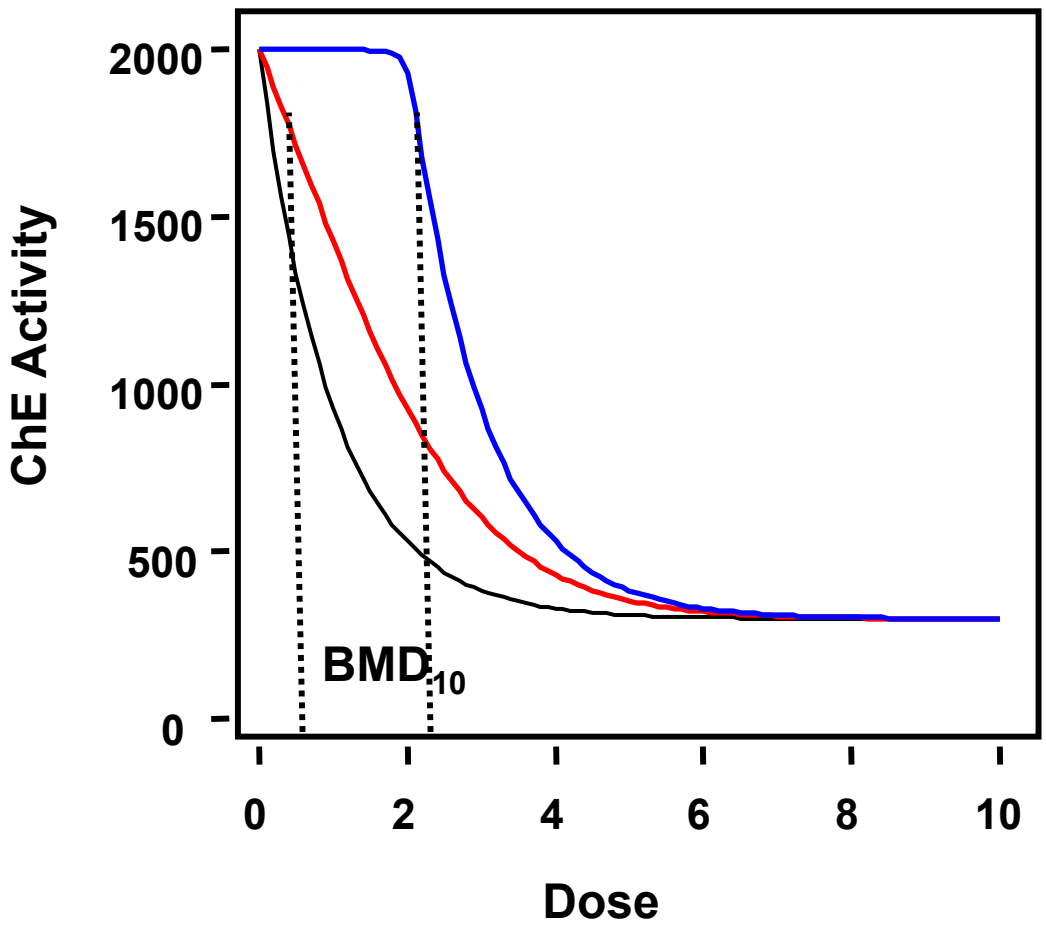
A is the background ChE activity,
m is the slope-scale factor,
$\boldsymbol{P_B}$ is the horizontal asymptote (i.e., limiting value of minimum cholinesterase activity),



Method for Modeling ChE Data

- **Joint Analysis**
  - All time points considered together
  - Exploration of low dose issues
  - Study to study variability in background ChE
  - All available data utilized

Method for Modeling ChE Data



Linear Low Dose Region

vs.

Flat Low Dose Region

Relative Potency Factors— Draft Revised CRA

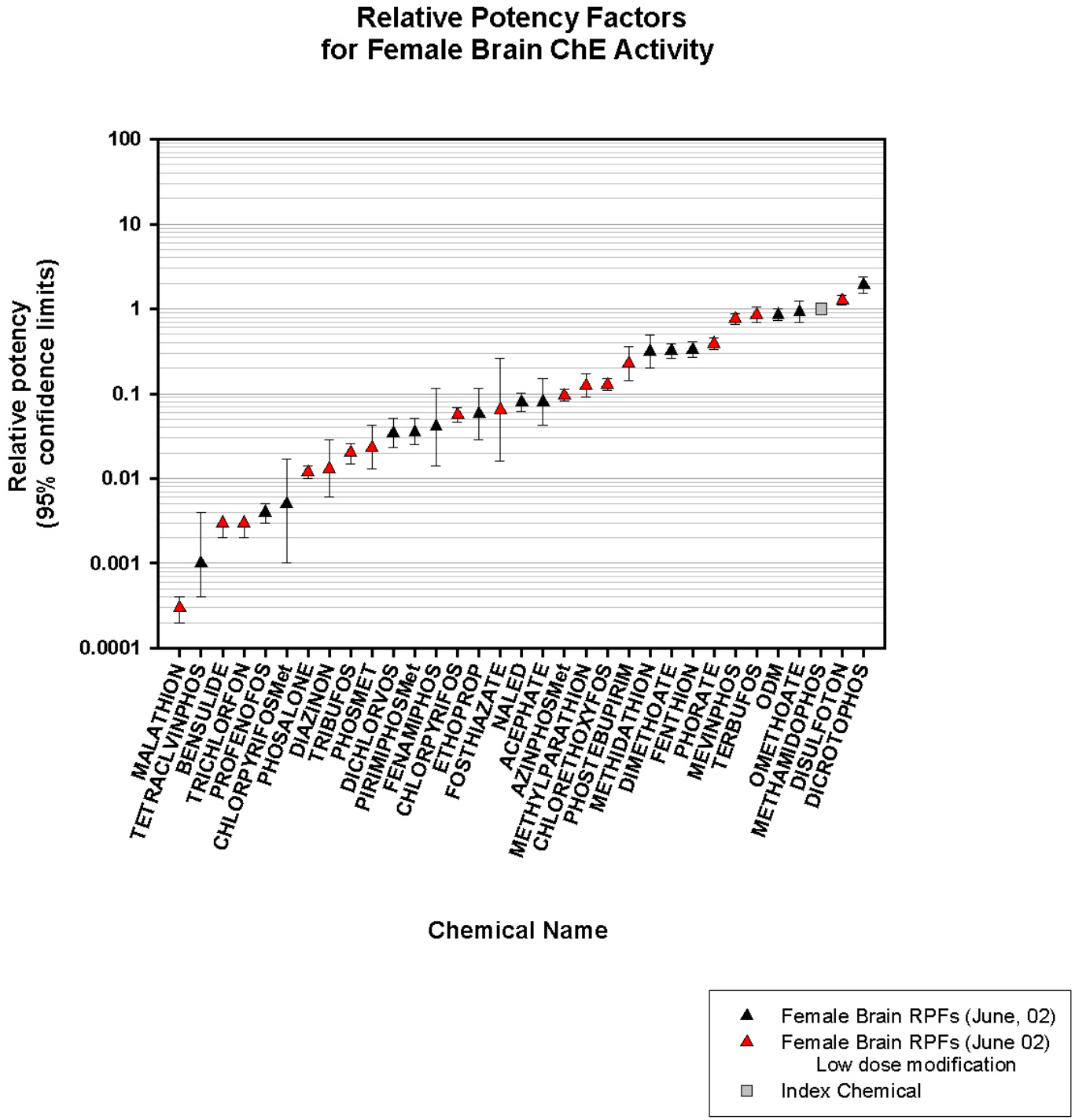


Table of RPFs

Relative Potency Factors for Female Brain Cholinesterase Activity	Oral	Dermal	Inhalation
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
Dichlorvos	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	0.003
Methamidophos	1.00	1.00	1.00
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	0.82
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	0.087

Points of Departure (PoDs)

PoDs for the Methamidophos BMD_{10}s and BMDLs		
Oral	0.08 mg/kg/day	0.07 mg/kg/day
Dermal	2.12 mg/kg/day	1.77 mg/kg/day
Inhalation	0.39 mg/kg/day	0.31 mg/kg/day

FQPA 10X Additional Safety Factor

FQPA 10X Safety Factor Provision

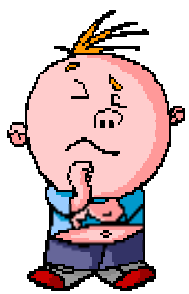
"in the case of threshold effects…an additional tenfold margin of safety …shall be applied for infants and children …"

"the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

FQPA Safety Factor Guidance

Guidance Structured Around 3 Areas of Analysis

1) Completeness of toxicity data
2) Degree of concern for pre-& postnatal toxicity
3) Completeness of exposure data



FQPA Safety Factor Determinations: Cumulative Risk Assessment

- **Analysis focuses on common mechanism of toxicity & associated effects in the young**

Status of FQPA 10X Factors

- Revised CRA:
  - 1X for Methamidophos, Chlorpyrifos and Dimethoate/Omethoate
  - 3X for All Others
- Incorporate FQPA 10X factors with RPFs
  - RPF x FQPA Factor = FQPA-Adjusted RPF
- SAP Meeting, June 2002

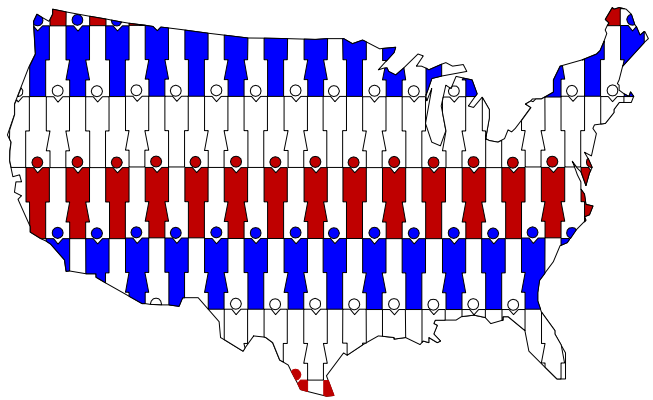
Food Assessment

Scope of Food Assessment

- 22 OP pesticides included
- Residues on many major foods analyzed
- Assume national diet

Populations Groups Assessed

- Separate assessments were based on survey information on the following age groups:
  - Children 1-2 years old
  - Children 3-5 years old
  - Adults 20-49 years old
  - Adults 50+ years old



Cumulative Dietary Exposure

Exposure = Residue X Consumption

Cumulative Residues

Relative Potency Factor Method

Chemical	RPF	Exposure (ppm)	Exposure Equivalents of Index (ppm)
A (index)	1	10	10
B	0.5	100	50
C	5	20	100
Total Exposure Equivalents of Index Chemical =			160 ppm

USDA PDP Monitoring Data

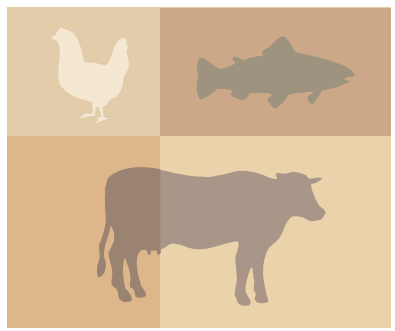
- Samples collected as closely as possible to point of consumption
- Statistically designed for use in dietary risk assessment and be representative of residue concentrations in U.S.
- Samples are prepared before analysis as if for consumption (e.g., cored, peeled)
- Children's foods are targeted.

USDA PDP Monitoring Data

- Commodities include:
  - Fresh market fruits and vegetables
  - Canned and frozen vegetable commodities
  - Grains
  - Dairy
  - Some processed commodities

Foods Based on FDA Monitoring Data

- Eggs
  - Assume negligible based on FDA monitoring data
- Seafood
  - Assume negligible based on FDA monitoring data
- Meat from Beef, Pork, Sheep & Goats
  - Used maximum residues found in FDA/TDS



The Proportion of the Diet of Children (1-2) Covered in the Cumulative assessment

Source of Residue Estimate	% of Diet
PDP	89.3
Translation of PDP	1.1
FDA	4.9
Assumed negligible	2.0
Not included	2.7

- The top four missing foods
  - Corn meal (0.50%)
  - Corn flour (0.49%)
  - Onion, dry bulb (0.38%)
  - Pinto beans (0.16%)

Cumulative Dietary Exposure

- Exposure = $Residue_{IE}$ X Consumption

CSFII 94-98

CSFII 1994-96/1998

- Intakes of individuals residing in U.S.
- 20,607 individual participants interviewed over two discontinuous days (~3-10 days apart)
- 1998 Supplemental Children's Survey
  - 5,559 additional children
  - Birth through 9 years old

Dietary Exposure Evaluation Model – DEEM-FCID™

- Probabilistic (Monte-Carlo) procedure
- Input:
  - Distributions for consumption
  - Distributions or point estimates for residue concentrations
- Output:
  - Distribution of one-day dietary exposures
    - 7, 14, 21, and 28-day dietary exposures calculated in DEEM/Calendex
  - Distribution of associated Margins of Exposure

Food: 7 Population Groups (1-Day)

	Exposure (mg/kg/day)			
	95th %	99th %	99.5th %	99.9th %
All infants < 1	0.0001	0.0003	0.0004	0.0009
Children 1-2	0.0002	0.0006	0.0009	0.0018
Children 3-5	0.0002	0.0005	0.0007	0.0015
Children 6-12	0.0001	0.0003	0.0004	0.0009
Age 13-19	0.0001	0.0002	0.0002	0.0005
Adults 20-49	0.0001	0.0002	0.0003	0.0005
Adults 50+	0.0001	0.0002	0.0003	0.0006

Analysis of Upper Portion of Exposure Distribution for Children 1-2

DEEM CEC

Top daily exposure records in distribution

- **Provides demographics on individuals**
- **Identifies the amount of foods consumed**
- **Identifies the residue level in each food**

Key Risk Estimate Elements

- Relatively few chemical/crop combinations play a major role in the OP cumulative risk assessment
- Not meant to imply that risks are such that exposure from any one chemical/crop combination must be addressed or that all of them must be addressed

Most Significant Chemicals In the Top 0.2 Percentile Of Exposure for Children 1-2

Chemical	Percentage of Total Exposure
Dimethoate/Omethoate	48 %
Azinphos-methyl	27%
Acephate/Methamidophos	11%
Methamidophos	5%
Phosmet	2.4%
Phorate	2.2%

Most Significant Foods In the Top 0.2 Percentile Of Exposure for Children 1-2

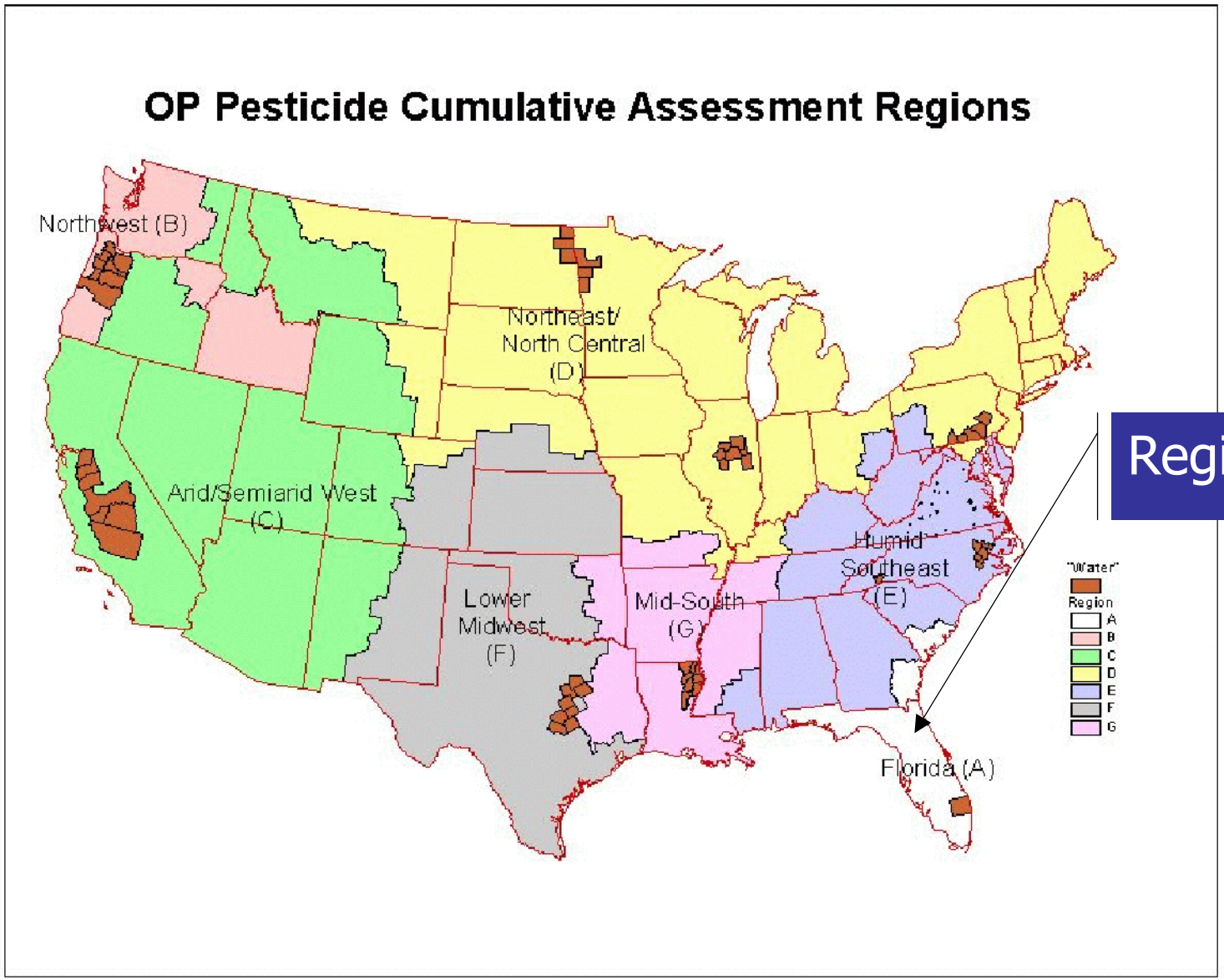
Food	Food Form	Fraction of Total
Grape	Uncooked; Fresh or N/S; Cook Meth N/S	0.33
Pear	Uncooked; Fresh or N/S; Cook Meth N/S	0.16
Apple, fruit with peel	Uncooked; Fresh or N/S; Cook Meth N/S	0.13
Apple, juice	Uncooked; Fresh or N/S; Cook Meth N/S	0.10
Tomato	Uncooked; Fresh or N/S; Cook Meth N/S	0.05
Grape, raisin	Uncooked; Dried; Cook Meth N/S	0.04
Bean, snap, succulent	Cooked; Frozen; Boiled	0.03
Pepper, bell	Uncooked; Fresh or N/S; Cook Meth N/S	0.03
Bean, snap, succulent	Cooked; Canned; Boiled	0.02
All Other Commodities		≤ 0.01

Drinking Water Assessment

Drinking Water Assessment

- Daily distributions of residues in water employed
- Regional (watershed) approach
- Accounted for non-agricultural areas in a watershed

Revised Regional Framework



Drinking Water Assessment

- Account for variations in source for drinking water
- Account for variations in time (daily, seasonally, yearly)
- Reflect co-occurrence of multiple chemicals as they occur together in place and time
- Provide distribution of daily concentrations for probabilistic exposure assessment

Drinking Water Assessment

- Location-specific environmental data (soil/site, weather, crops)
- Major crop-OP combinations within that area
  - Crops that actually occur together
  - OPs that are actually used on those crops
  - Account for approximately 95% of OP use in area

Drinking Water: Results

- Drinking water is not a major contributor to total cumulative risk

Residential Exposure Assessment

Residential Exposure

- Residential use reduced by >20 million pounds annually
- Principally as the result of risk mitigation for chlorpyrifos and diazinon
- Includes remaining residential OPs that have significant exposure and exposure data

Residential Exposure

- Started with 17 OPs with residential/public area uses
- 7 OPs excluded from cumulative assessment because residential uses were eliminated/reduced to a negligible level
- Of the remaining 10, two are limited to public health uses (naled, fenthion)
- 3 OPs with residential/public area uses still under review (DDVP, malathion, tetrachlorvinphos)

Residential Exposure Assessment

Indoor Use:	DDVP (pest strip use in closets and cupboards)
Pet Use:	Tetrachlorvinphos (spray/dip/powder)
Home Lawns:	Bensulide, Trichlorfon
Golf Course:	Acephate, Bensulide,Fenamiphos, Trichlorfon

Residential Exposure

Home Garden: Acephate and Disulfoton ornamental), Malathion (ornamental and edible food)

Public Health: Fenthion, Malathion, Naled

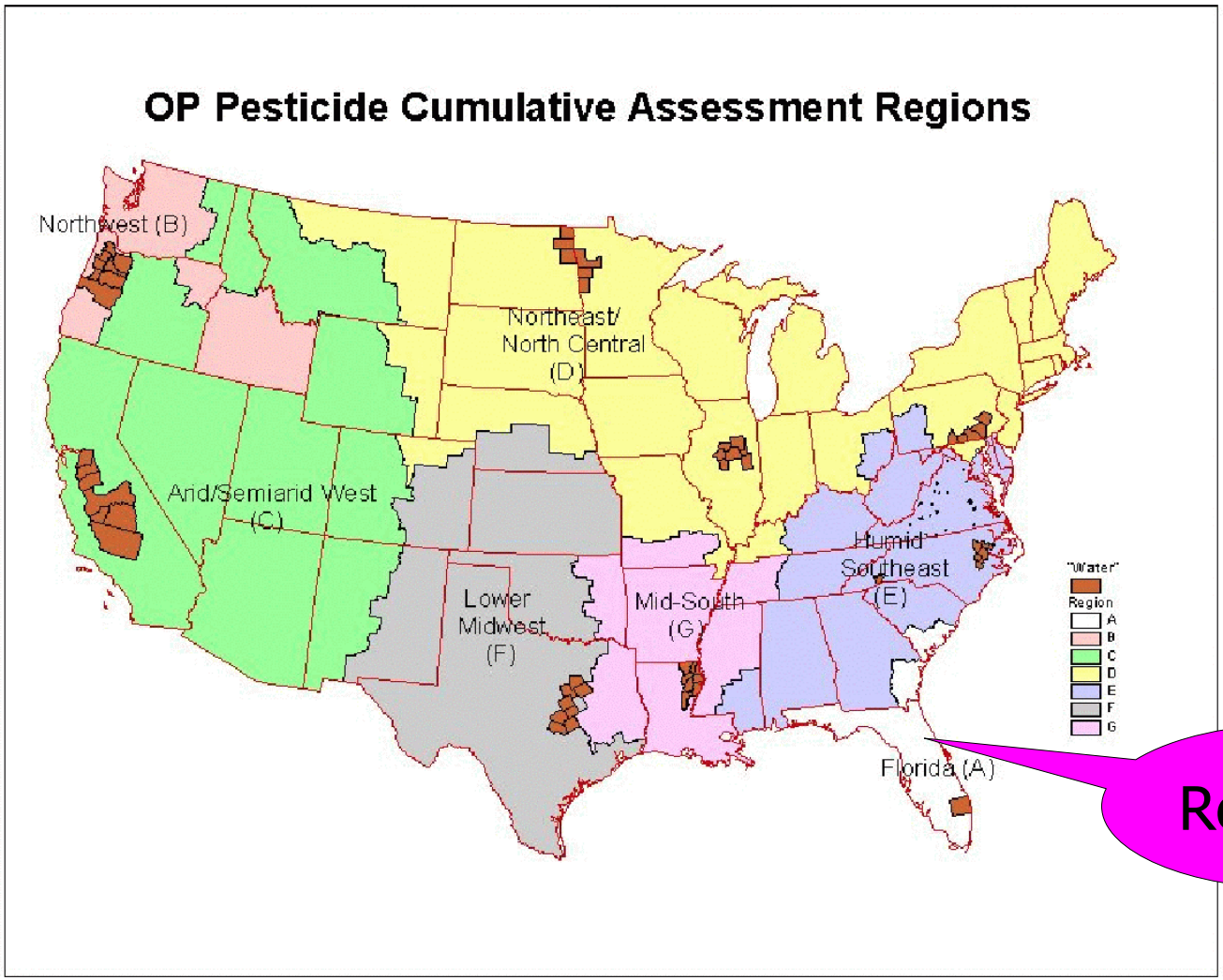
Residential Exposure

Assessment performed for the following age groups:

- Children 1-2 years old
- Children 3-5 years old
- Adults 20+

All ages assessed for Region A

Conducted for 7 distinct geographical regions


OP Pesticide Cumulative Assessment Regions
Northwest (B)
Northeast/
North Central
(D)
Arid/Semiarid West
(C)
Lower
Midwest
(F)
Mid-South
(G)
Humid
Southeast
(E)
Florida (A)
"Water"
Region
A
B
C
D
E
F
G

Region A

Residential Exposure: Region A

- Lawn - DDVP, Malathion, Trichlorfon
- Golf courses - Acephate, Bensulide, Fenamiphos, Malathion
- Ornamental gardens - Acephate, Disulfoton, Malathion
- Home gardens - Malathion
- Indoor - DDVP (pest strips and crack and crevice)
- Public health - Fenthion, Malathion, Naled

Residential Exposure

- Use of distributions for residues and exposure elements
- Use of a calendar based model to address the temporal use of residential OP's
  - Calendex™
- Use of distributions for residues and exposure elements
- Use of survey data and other pesticide use information

Residential Exposure: Information and Data Used

- Various use surveys
- Chemical specific data on transfer of residues
- Types of clothing
- Behavioral information
  - Hand-to-mouth
  - Choreographed adult activities
  - Non-scripted play

Residential Exposure: Results

- Use of DDVP in No-Pest strips major contributor to exposure
  - Only remaining indoor use of OPs
  - Removal of DDVP from assessment in sensitivity analysis resulted in MOEs approximately the same as for food alone

Cumulative Risk:

Put It All Together

Expression of Cumulative Risk: Margin of Exposure (MOE)

$$MOE = \frac{POD\ (mg/kg/day)}{Exposure\ (mg/kg/day)}$$

Key Concepts in Cumulative Assessment

- Important to "integrate" or combine these estimated exposures in an internally consistent manner to develop region-specific risk picture
  - Integrated (or Combined) Exposure = "Total MOE"
  - "Appropriate Matching and Combining"

$$MOE_{total} = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{oral}} + \frac{1}{MOE_{inhalation}}}$$

Key Concepts in Cumulative Assessment:

"Appropriate Matching and Combining"

- **Objective:** to appropriately match and subsequently combine estimates of pesticide exposures through food with estimates of pesticide exposures through residential uses and estimates of exposures through drinking water

Key Concepts in Cumulative Assessment:
Appropriate Matching and Combining

- In summary, must track potentially exposed persons on a daily basis in a way that preserves all appropriate linkages in a way that considers time, region, and age groups

DEEM™/Calendex™ Cumulative Assessment

- DEEM™/Calendex™ provides a probabilistic assessment in which appropriate matching occurs
  - Incorporates concept of a Calendar to evaluate aggregate exposures
  - Looks at each individual day of the year
    - Allows appropriate "temporal matching" of exposures through food, drinking water, and residential pathways.
    - Temporal aspect of exposure through residential and agricultural uses important for OP pesticides due to expected seasonal use-patterns

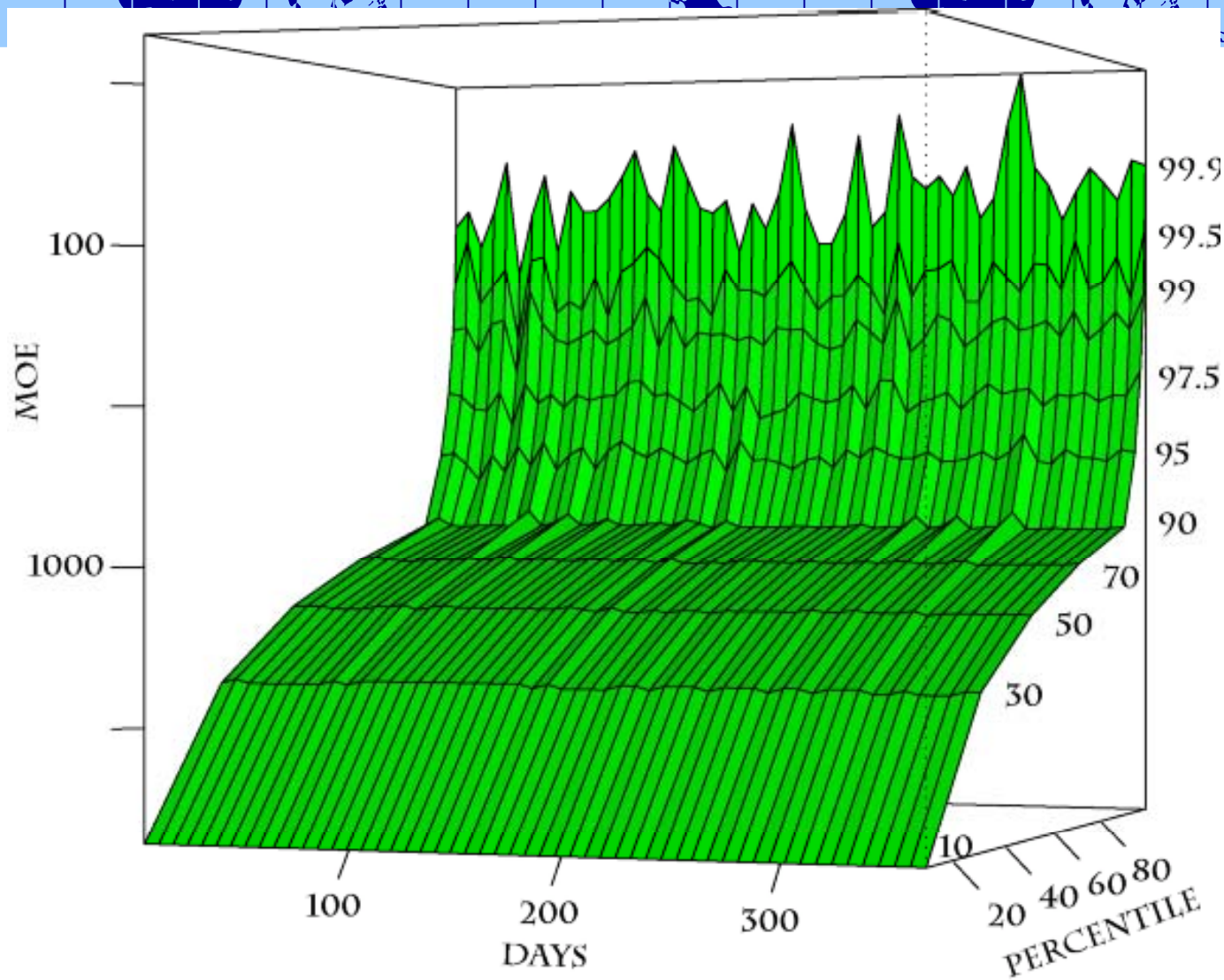
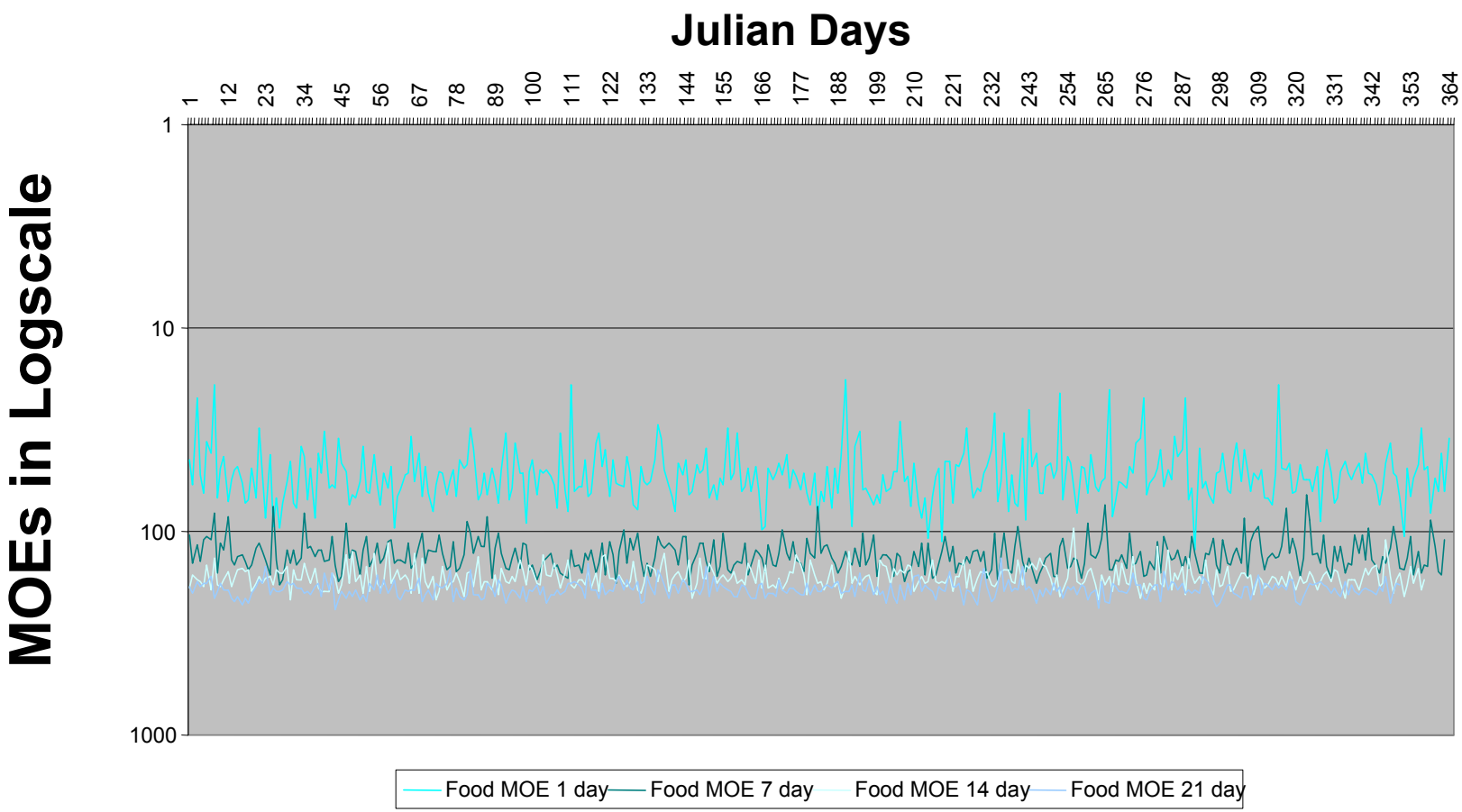
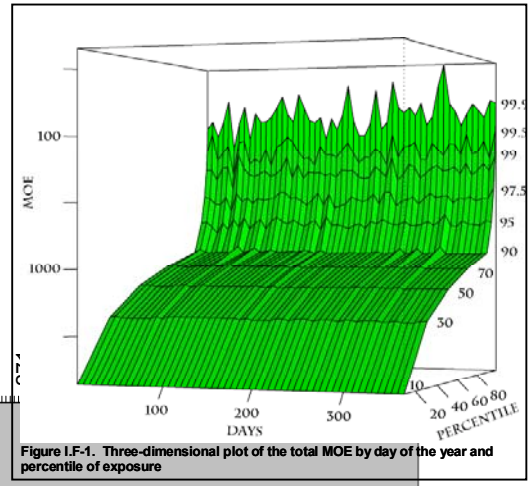


Figure I.F-1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure

Comparison of Exposure Windows in the Cumulative: Food Only



Example of Calendex™ Analysis (time based exposure profile)



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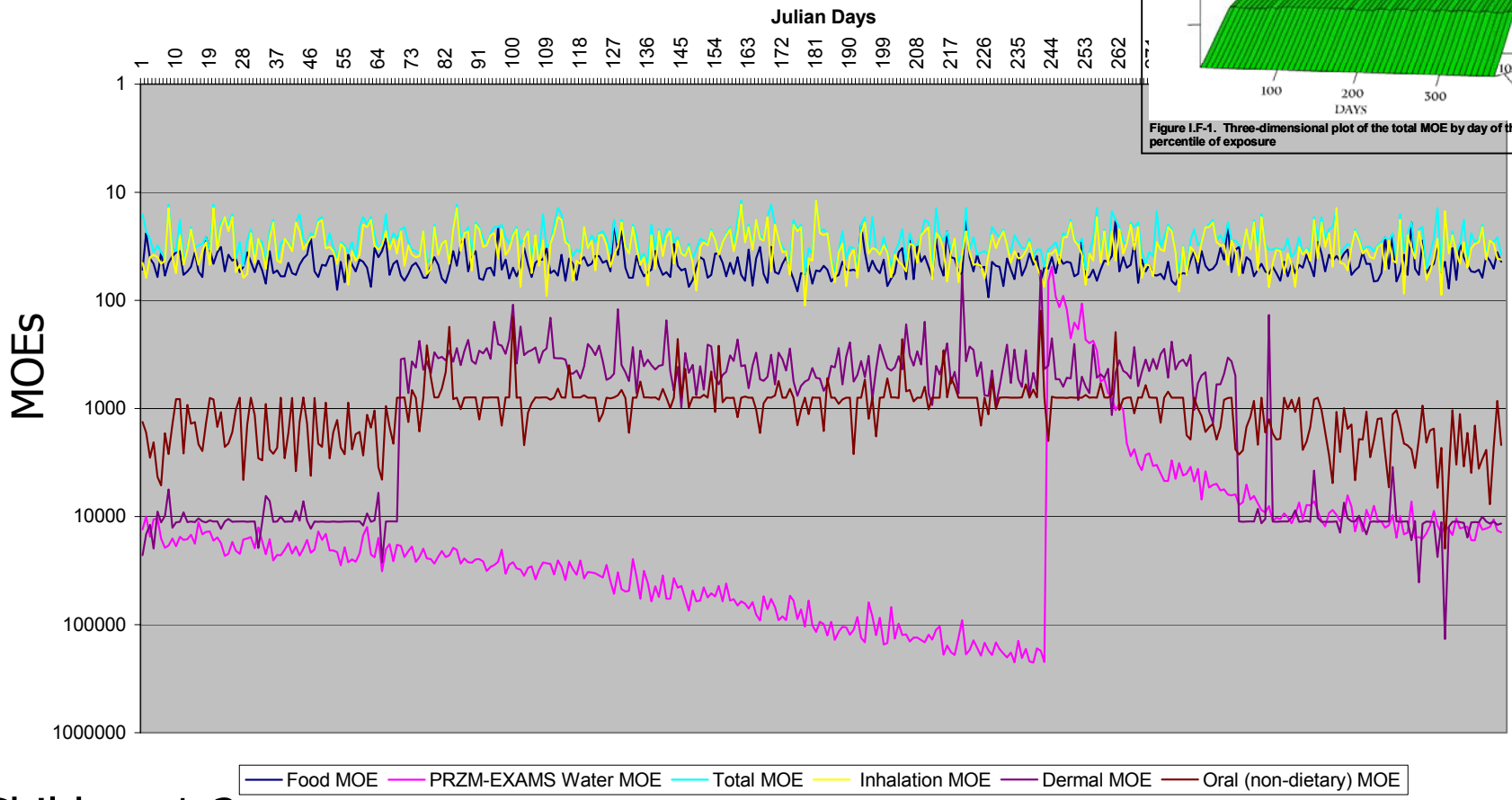
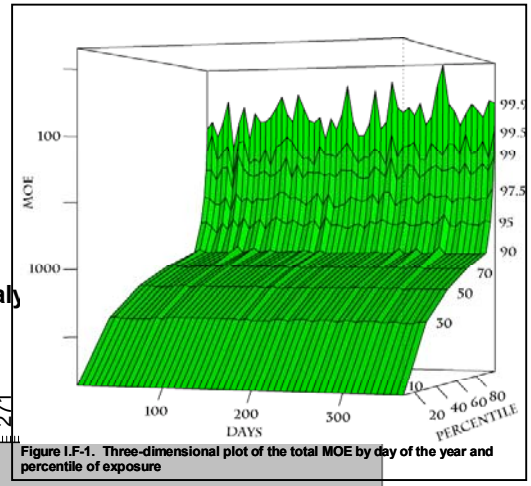
Cumulative MOEs for Children 1-2 Region A One Day Analysis



Children 1-2
1-day

Day of the Year

Example of Calendex™ Analysis (time based exposure profile)



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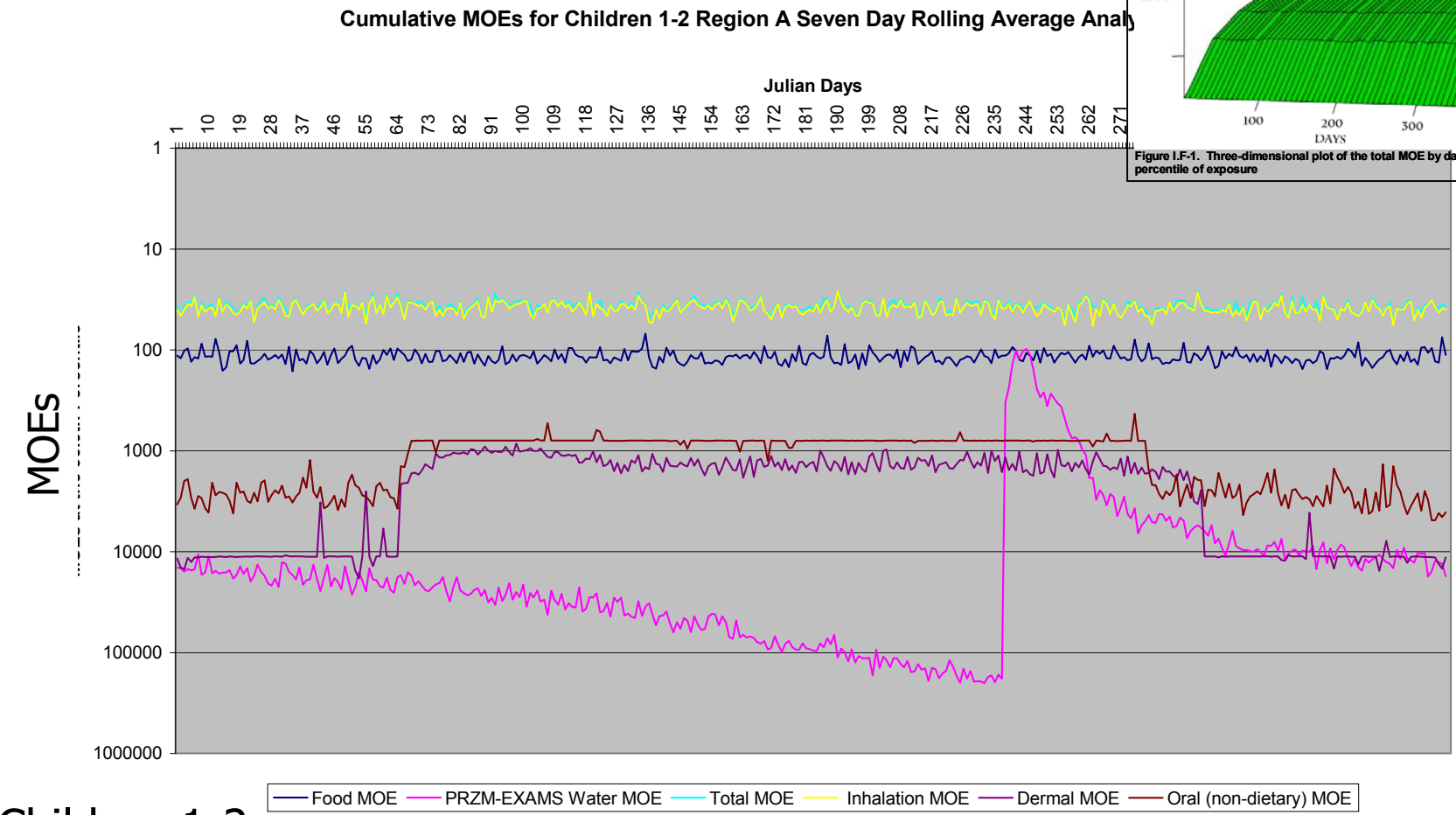

Children 1-2
7-day

Day of the Year

Summary

- Food, water, and residential exposures were considered probabilistically in the cumulative assessment
  - Reflects realistic pesticide use based on pest pressures, weather, activity patterns, etc.
  - Temporal and spatial characteristics were preserved and maintained to produce realistic assessments

Summary

- Result of Assessment is a time based exposure profile of exposures at any selected percentile
  - Total Exposure
  - Various pathway specific exposures

Risk Characterization Conclusions

- OPP advanced risk assessment methods as it developed OP cumulative assessment
  - State of the art
- Extensive peer review of methods and assessment
- Risk mitigation efforts have reduced exposure.
  - Some single chemical assessments not yet complete.

What's Next for Cumulative in OPP?

- Other Common Mechanism Groups:
  - N-methyl carbamates
  - Triazines
  - Chloracetanilides